The Effect of Concomitant Use of Colony-Stimulating Factors on Bleomycin Pulmonary Toxicity – A Systematic Review and Meta-Analysis

Seyed Mahdi Seyedzadeh Sani [1†], Mehrdad Sahranavard [1†], Mahdi Jannati Yazdanabad [2], Mohsen Seddigh Shamsi [3], Sepideh Elyasi [1], Amir Hooshang Mohammadpour [1], Thozhukat Sathyapalan [4], Omid Arasteh [1*], Vahid Ghavami [1*], Amirhossein Sahebkar [5,6,7,8*]

[1]Department of clinical pharmacy, School of pharmacy, Mashhad University of medical science, Mashhad, Iran;

[2]Department of Biostatistics and Epidemiology, School of health, Mashhad University of medical science, Mashhad, Iran;

[3]Department of Hematology Oncology, Faculty of medicine, Mashhad University of medical science, Mashhad, Iran;

[4] Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, UK

[5] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.

[6] Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

[7] School of Medicine, The University of Western Australia, Perth, Australia.

[8] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

***Corresponding Authors**: arasteho@yandex.com; gavamiv@yandex.com; amir_saheb2000@yahoo.com

Funding: None

Competing interests: None

Abstract

Background: Changes in the incidence of bleomycin pulmonary toxicity (BPT) as a result of adding colony-stimulating factors (CSF) to bleomycin regimens has been investigated in numerous studies. We performed a systematic review and meta-analysis to assess the outcomes of these studies.

Methods: A systematic search was performed using Pubmed, Scopus, Web of Science, and Embase on April 2021. Studies evaluating the incidence of BPT in patients receiving bleomycin with and without CSF were included. In addition, meta-analysis was performed by pooling odds ratios using R.

Results: Out of 340 obtained records, our qualitative and quantitative analysis included 3234 and 1956 patients from 22 and 14 studies, respectively. The quantitative synthesis showed that addition of CSF significantly increased the risk of BPT incidence (OR = 1.82, 95% CI: 1.37-2.40, $p<0.0001$; $I2 = 10.7\%$). Subgroup analysis did not show any association between continent, bleomycin dose, cancer type, type of study, and pulmonary function test with BPT incidence.

Conclusion: This systematic review and meta-analysis showed that co-administration of CSF with bleomycin increases the incidence of BPT. The physicians need to consider this finding while deciding the best strategy for this cohort of patients.

Keywords:

Bleomycin, colony-stimulating factor, bleomycin pulmonary toxicity

1. Introduction:

Bleomycin is a member of the glycopeptide antibiotics family and is a chemotherapeutic agent produced by *Streptomyces verticillus* (1, 2). Bleomycin has received FDA approval for treating Hodgkin's and non-Hodgkin's lymphoma, germ cell tumours, and malignant pleural effusion (3-7). Its off label indications include vascular anomalies and warts (5). The reported adverse effects of bleomycin are genotoxicity, local hyperpigmentation, nausea, vomiting, neuropathy, neutropenia, and lung toxicity (8-11). Bleomycin's most dangerous side effect, pulmonary toxicity, can occur through interstitial capillary edema, overproduction of surfactant, and mediators release. Various studies have reported bleomycin pulmonary toxicity (BPT) prevalence of 2-46%, with a mortality rate of 1-2% among bleomycin administered patients (9). BPT incidence risk factors include age, where it is established that people over 40 years old can experience BPT more than others. However, a study didn't find any relationship between age and BPT (12, 13). 2) Low renal clearance is another risk factor for BPT since renal clearance is essential in bleomycin elimination (14). The other risk factors for BPT include cumulative bleomycin dose more than 400 U (15), cigarette smoking (16, 17), inflammatory markers such as Prognostic Nutritional Index score <40 and pre-chemotherapy neutrophil-to-lymphocyte ratio ≥6 (18), a high fraction of inspired oxygen (FiO2). (19, 20), other chemotherapy drugs like cisplatin and gemcitabine (21, 22) and thoracic irradiation (22). Animal studies have shown the use of colony-stimulating factors like granulocyte colony-stimulating factor (G-CSF) as a risk factor for BPT; however, its effect has remained controversial in human studies (4, 18, 23-30).

Colony-stimulating factors (CSF), including Granulocyte/Macrophage Colony Stimulating Factor (GM-CSF) and G-CSF, are used in patients with a higher than 20% risk of neutropenia incidence (primary prophylaxis) and patients with febrile neutropenia in a chemotherapy cycle (secondary prophylaxis). Moreover, G-CSF (filgrastim) has FDA approval for congenital neutropenia. In addition, PEGylated G-CSF is approved to support neutropenia and GM-CSF (sargramostim) is approved for neutropenia induced by transplantation of stem cells (10, 31). Neutropenia is known as neutrophil counts below 1500/µl. Chemotherapy-induced neutropenia is related to relatively high mortality, morbidity, and additional health costs (32).

While the effect of CSF application in avoidance of neutropenia is apparent, controversial evidence indicates its addition to bleomycin regimens as a risk factor for BPT incidence. This review attempts to solve the controversies in the literature by a systematic review and meta-analysis comparing bleomycin-administered patients who received CSF and those who did not.

2. Methods:

This study was performed to solve antithesis reports around the exacerbation effect of CSF co-administration on BPT incidence. The study protocol was registered with PROSPERO (CRD42021267331).

2.1. Search strategy and selection criteria:

MeSH (Medical Subject Heading) terms and entry terms relating to the topic were used to define search strategy. The most important terms were "neoplasm", "Granulocyte colony-stimulating

factor", "bleomycin", and "Pulmonary fibrosis". The search was performed using Pubmed, Scopus, Web of Science and Embase on April 2021. We didn't apply any time, language or study design restriction. Also, a search alert was activated to inform authors of new articles related to the search strategy. The detailed search strategy is provided in supplementary materials (Table S1).

2.2. Eligibility criteria:

Human studies with these criteria were included: (1) having a control group, received bleomycin without CSF, (2) having a case group, received bleomycin and CSF and (3) assessed BPT as an outcome.

2.3. Data Extraction and Management:

Screening (SMSS and MJY), full-text assessment (SMSS and MJY), data extraction (SMSS and MS), and quality and risk of bias assessment (SMSS and MS) were performed by two reviewers independently. Disagreements were resolved through discussion or consult of the third reviewer (OA). Extracted items were: name of the first author, publication date, country, type of study, follow-up period duration, cancer type, chemotherapy regimen, the dose of bleomycin and colony-stimulating factors, pulmonary test for toxicity detection (functional and others), effect size or the number of BPT patients in CSF and non-CSF groups to calculate the effect size. Data is extracted in standard form on Excell office 2016.

2.4. Quality and Risk of bias assessment:

The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of observational studies. Studies in meta-analyses were ranked as good, fair, and poor quality, regarded as 1-3, 4-6, 7-9 scores, respectively (33). Also, for assessing the quality of clinical trials, the Cochrane risk of bias assessment tool was used (34).

2.5. Statistical analysis:

We extracted the natural logarithm of odds ratios (OR) and its standard error from the studies to measure the association between concomitant use of CSF and BPT. When available, adjusted OR estimates were selected over crude measures. Since the reported effect size in the Binder et al. study was hazard ratio, we calculated the OR and its confidence interval based on the raw data (35). The Q-test and the I^2 statistic were employed for assessing the between-study heterogeneity (11, 34). The I^2 score values of 0% to 40% were considered not important (36). Based on the results of Cochran's Q test and I^2 statistic, the presence of heterogeneity was rejected, and the effect sizes were pooled by using the inverse variance weighted mean of the natural logarithm of ORs with 95% CIs. To investigate the presence of outliers, we compared the confidence intervals of the studies with the confidence interval of the pooled effect size (37). A leave-one-out sensitivity analysis was performed to check for the robustness of the pooled estimate (38). Subgroup analyses were carried out by adjustment of studies for the place of study (America, Asia and Europe continents), cumulative bleomycin dose (less than 150 or 200 mg and more than 150 or 200 mg) because the skin side effect reported at these doses (39), performed the pulmonary functional test (yes and no) and type of study (case-control, cohort and clinical trials). In addition, we used the Q

test to determine if the subgroup differences are large enough not to be explainable by sampling error alone. We fitted a meta-regression to evaluate the association between publication year and duration of the studies and the pooled effect size. We employed funnel plots, and both Egger's (40) and Begg's (41) tests to evaluate the publication bias. We performed the meta-analysis in R software (https://cran.r-project.org) using packages meta, metafor, and dmetar (37, 42, 43).

3. Result:

3.1. Study description:

As illustrated in Figure 340 records were obtained, including 21 from Pubmed, 215 from Scopus, 42 from Web of Science, 60 from Embase provided by performed search strategy and two records provided by manual search. After removing 59 duplicate records, 281 records were screened, resulting in the elimination of 249 irrelevant records. Full-text assessment of the remaining 32 records led to the exclusion of 10 studies due to not having the required case or control group in 6 studies, inclusion the of study patients in another updated paper in 3 studies, and not assessing BPT as an outcome in one study. Finally, 22 studies were included in our systematic review, and of these, 14 studies reported enough data to enter the meta-analysis.

Studies included in the systematic review were 16 cohort studies (3, 4, 6, 7, 28, 44-54), 4 case-control studies (26, 55-57) and 2 clinical trials (24, 58) (Table 1). Different diagnosis and chemotherapy regimens were used in eligible studies. Cancer types of patients were Hodgkin's lymphoma (HL) or classical Hodgkin's lymphoma (cHL) in 8 studies (6, 7, 26, 28, 47, 49, 51, 54), germ cell tumor (GCT) in 8 studies (4, 24, 45-47, 50, 52, 53), non-Hodgkin lymphoma in 2 studies (3, 58), HL or GCT in 2 studies (56, 57), and lymphoma with no specific reported type in 2 studies (44, 55). ABVD, BEP, and other different chemotherapy regimens were used. Continents in which studies were performed were America in 10 studies (4, 6, 7, 26, 28, 46, 50-52, 57), Asia in 6 studies (3, 44, 45, 53, 55, 56) and Europe in 6 other studies (24, 47-49, 54, 58). Different BPT diagnosis criteria and tests were used in different studies (Table S2). More commonly performed pulmonary functional tests were diffusing capacity for carbon monoxide (DLCO) (7, 28, 47, 48, 53, 55, 56, 58) and the partial pressure of oxygen in the arterial blood (PaO_2) (3, 44) and more commonly performed other evaluations were chest X-ray (CXR) (7, 26, 44, 45, 52, 53, 55) and computed tomography (CT) scan (26, 28, 44, 45, 47, 52, 53, 55). Studies used Quality assessment of observational studies classified two studies as fair quality (44, 49) and 18 studies as high quality (3, 4, 6, 7, 26, 28, 45-48, 50-57). Also, results of Cochrane's risk of bias assessment tool on 2 clinical trial studies are demonstrated in supplementary materials (Table S5, Figure S1) (24, 58). Risk factorsthat have benn given in each study for the possibility of impact on the occurrence of BPT, except for CSF listed in appendix (Table S4).

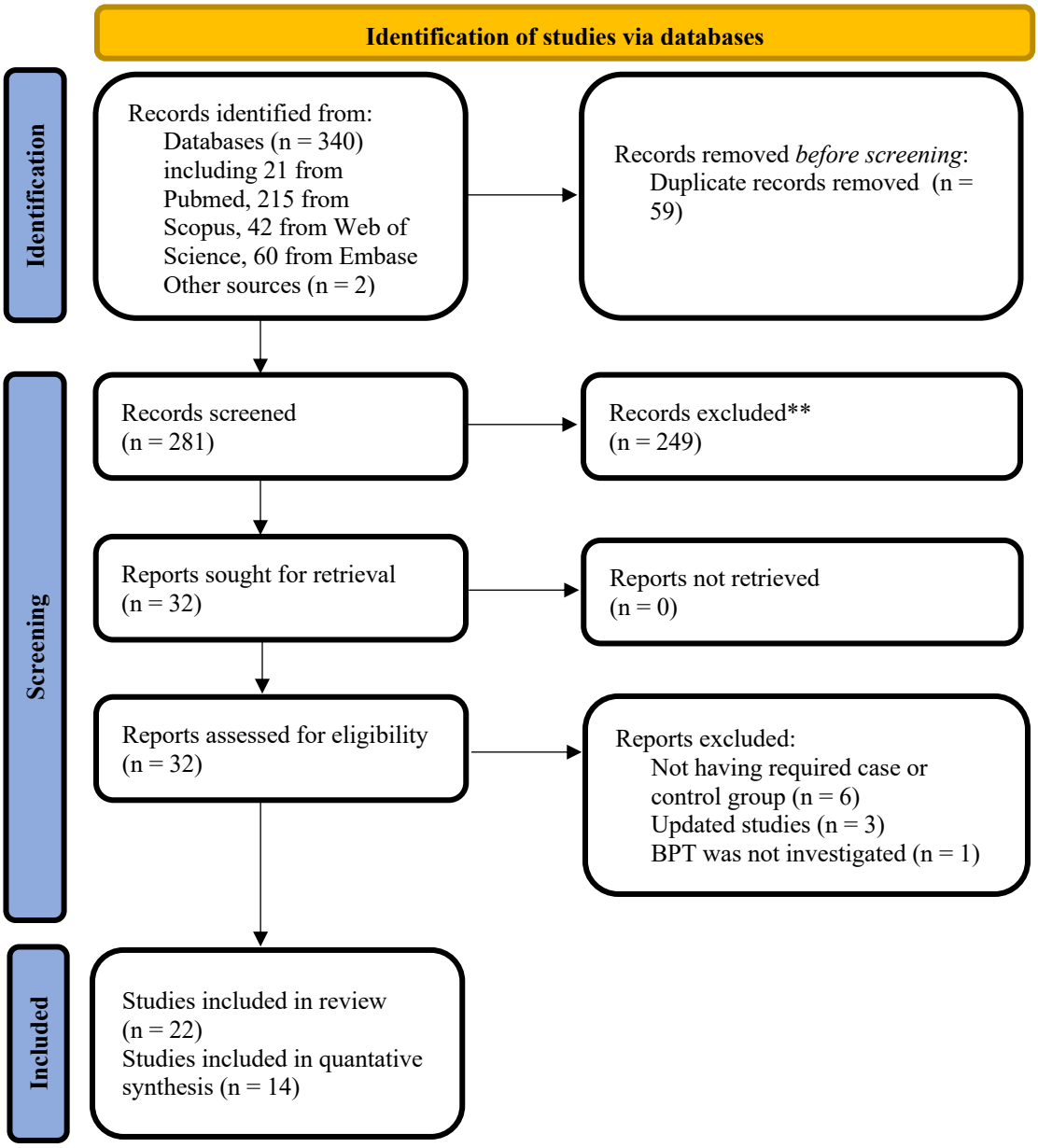

Figure 1. Prisma flow diagram for study selection (59).

Table 1: Characteristics of eligible studies.

Study	Place of study (country and continent)	design	Inclusion criteria	Main diagnosis	Chemotherapy regimen	Total population of analysis	Stratification Based on Controlled Variables	Test for assessment of pulmonary toxicity	Quality of article
Iki et al. (1993) (44)	Japan (Asia)	Cohort	Patients with no significant change in the schedule of treatment in 1988-1991	Malignant lymphoma	NR	75	No adjusted effect size	Paraclinical and functional tests	Fair
Bastion et al. (1994) (58)	France and Belgium (Europe)	Clinical trial	reporting two studies on the patient treated by Bleomycin and GCSF. The age of patients was <55 years in one study and 55-70 in the other.	Non-Hodgkin's lymphoma	NR	278	No adjusted effect size	Functional tests	*
Lei et al. (1994) (3)	China (Asia)	Cohort	NHL patients received BACOP with no history of pulmonary disease or cancer therapy.	Non-Hodgkin's lymphoma	BACOP	36	No adjusted effect size	Paraclinical and functional tests	Good
Saxman et al. (1997) (4)	USA (America)	Cohort	Advanced GCT patients treated by bleomycin included chemotherapy regimens with the age range of 15-48. Controls are advanced GCT patients treated by phase III study (twice the dose of cisplatin) to compare with standard BEP and age range of 14-49.	Germ cell tumor (GCT)	Control: BEP case : etoposide, ifosfamide, cisplatin, vinblastine, and	86	No adjusted effect size	Paraclinical tests	Good

					bleomycin				
Fossa, Sophie *et al.* (1998) (24)	United Kingdom (Europe)	Randomized clinical trial	Previously untreated histologically proven non-seminomatous GCT and poor prognosis.	Germ cell tumor	BEP/EP or BOP/VIP-B	257	No adjusted effect size	NR	*
Martin *et al.* (2005) (26)	USA (America)	Case-control	newly diagnosed, biopsy-proven HL	Hodgkin's lymphoma	ABVD, MOPP-ABV(D), COPP-ABV(D), BEACOPP, and Stanford V	141	No adjusted effect size	Paraclinical tests	Good
Zahid *et al.* (2009) (45)	Pakistan (Asia)	Retrospective cohort	GCT patients from March 2006 to September 2008	Germ cell tumor	BEP	83	adjusted effect size	Paraclinical tests	Good
Tran *et al.* (2012) (46)	Canada (America)	Retrospective cohort	GCT patients receiving first-line chemo in 2000-2010	Germ cell tumor	NR	260	adjusted effect size	NR	Good
Ahmed and Al-Zakwani (2013) (55)	Oman (Asia)	Case-control	Patients used bleomycin at least one dose at SQUH in 2007- 2010	Hodgkin's lymphoma in 67% of patient	ABVD in 63% of patients	46	No adjusted effect size	Paraclinical and functional tests	Good
Alexander *et al.* (2013)	Portugal (Europe)	Retrospective cohort	GCT patients treated by BEP in 2000-2012	Germ cell tumor	BEP	114	No adjusted effect size	Paraclinical and functional	Good

(47)								tests	
Santos *et al.* (2013) (48)	Portugal (Europe)	Retrospective cohort	HL patients received ABVD in 2010-2011	Hodgkin's lymphoma	ABVD	65	No adjusted effect size	Paraclinical and functional tests	Good
Marri et al. (2014) (6)	USA (America)	Retrospective cohort	CHL patients treated with bleomycin-consisted chemotherapy in 2000-2012	classical Hodgkin's Lymphoma (cHL)	Not recorded	161	No adjusted effect size	Paraclinical and functional tests	Good
Stamatoullas *et al.* (2014) (49)	France (Europe)	Retrospective cohort	Classical HL patients older than 60 years old, referred to Saint-Louis hospital in 1997-2012	Classical Hodgkin's Lymphoma	ABVD	147	No adjusted effect size	NR	Fair
Ko *et al.* (2015) (50)	Canada (America)	Retrospective cohort	consecutive metastatic testicular germ cell tumor patients receiving first-line chemotherapy in 1990-2013	malignant testicular germ cell tumor	BEP	275**	No adjusted effect size	Functional tests	Good
Yao *et al.* (2016) (51)	USA (America)	Retrospective cohort	HL patients treated by ABVD, some of them received pegylated filgrastim	Hodgkin's lymphoma	ABVD	69	No adjusted effect size	Paraclinical tests	Good
Binder *et al.* (2017)	USA (Americ	Retrospective	HL patients receiving at least one	Hodgkin's	ABVD	54	Adjusted	Paraclinical and	Good

(7)	a)	cohort	dose of bleomycin in 2003-2015	lymphoma			effect size	functional tests	
Kwan *et al.* (2017) (52)	Canada (America)	Retrospective cohort	GCT patients received chemotherapy in 2000-2010	Germ cell tumor	BEP	212**	Adjusted effect size	Paraclinical tests	Good
Sun *et al.* (2017) (28)	Canada (America)	Retrospective cohort	HL patients treated with ABVD in 1999-2009	Hodgkin's lymphoma	ABVD	253	Adjusted effect size	Paraclinical and functional tests	Good
Maruyama *et al.* (2018) (53)	Japan (Asia)	Retrospective cohort	GCT patients underwent BEP in 2008-2017	Germ cell tumor	BEP	52	No adjusted effect size	Paraclinical and functional tests	Good
Tayshetye *et al.* (2018) (56)	Japan (Asia)	Case-control	Bleomycin treated patients in 2008-2016	Hodgkin's lymphoma or testicular germ cell tumor	NR	83	NR	Functional tests	Good
Andersen *et al.* (2018) (54)	Denmark (Europe)	Cohort	HL patients treated with bleomycin containing chemotherapy in 1990-2014	Hodgkin's lymphoma	ABVD	409**	No adjusted effect size	Paraclinical tests	Good
Laprise-Lachance *et al.* (2019)	Canada (America)	Nested case-control	GCT patients treated by BEP and HL patients treated by ABVD in 2000-2016	Hodgkin's lymphoma or testicul	ABVD or BEP	78**	Adjusted effect size	Paraclinical tests	Good

(57)				ar germ cell tumor					

NR: not reported. BACOP: Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine and prednisone. BEP: Bleomycin, Etoposide, Cisplatin. BOP/VIP-B: Bleomycin, Vincristine, Cisplatin/Etoposide, Ifosfamide, cisplatin-Bleomycin. ABVD: Adriamycin, Bleomycin, vinblastin, Dacarbazine. MOPP-ABV(D): Mechlorethamine/Vincristine/Procarbzine/Prednisone–Doxorubicin/Bleomycin/Vinblastine (Vacarbazine); COPP-ABV(D): Cyclophosphamide/Vincristine/Procarbazine/Prednisone–Doxorubicin/Bleomycin/Vinblastine (Dacarbazine); BEACOPP: Bleomycin/ Etoposide/Doxorubicin/Cyclophosphamide/Vincristine/Procarbazine/Prednisone; StanfordV: Doxorubicin/Vincristine/Vinblastine/Bleomycin/ Mechlorethamine/Cyclophosphamide/Etoposide/Prednisone. *Quality assessment of clinical trials recorded in appendix file. **In Ko *et al.* (2015) (50), Kwan *et al.* (2017) (52), Andersen *et al.* (2018) (54) and Laprise-Lachance *et al.* (2019) (57) total population was 346, 260, 412 and 88 but 275, 212, 409 and 78 of the patients were reported as received bleomycin with or without G-CSF, respectively.

3.2. Association of concomitant use of colony-stimulating factors and bleomycin with BPT incidence

The data of 14 studies with a total sample size of 1956, including more than 1093 cases and more than 777 controls (Table S3), were entered into the meta-analysis. Based on the pooled data, concomitant use of colony-stimulating factors is a risk factor for BPT incidence (OR = 1.82, 95% CI: 1.37-2.40, p<0.0001; I2 = 10.7%, Q = 14.55, p=0.336) (Table 1 and Figure 2).

We calculated the OR of the Zahid 2009 study according to the reported confidence interval. Its confidence interval is so wide (1.83-178.6); however, in other studies, the lower limit is 0.43, and the upper limit is 12.79, so the weight of the article is considered low, as shown in the forest plot (Figure 2).

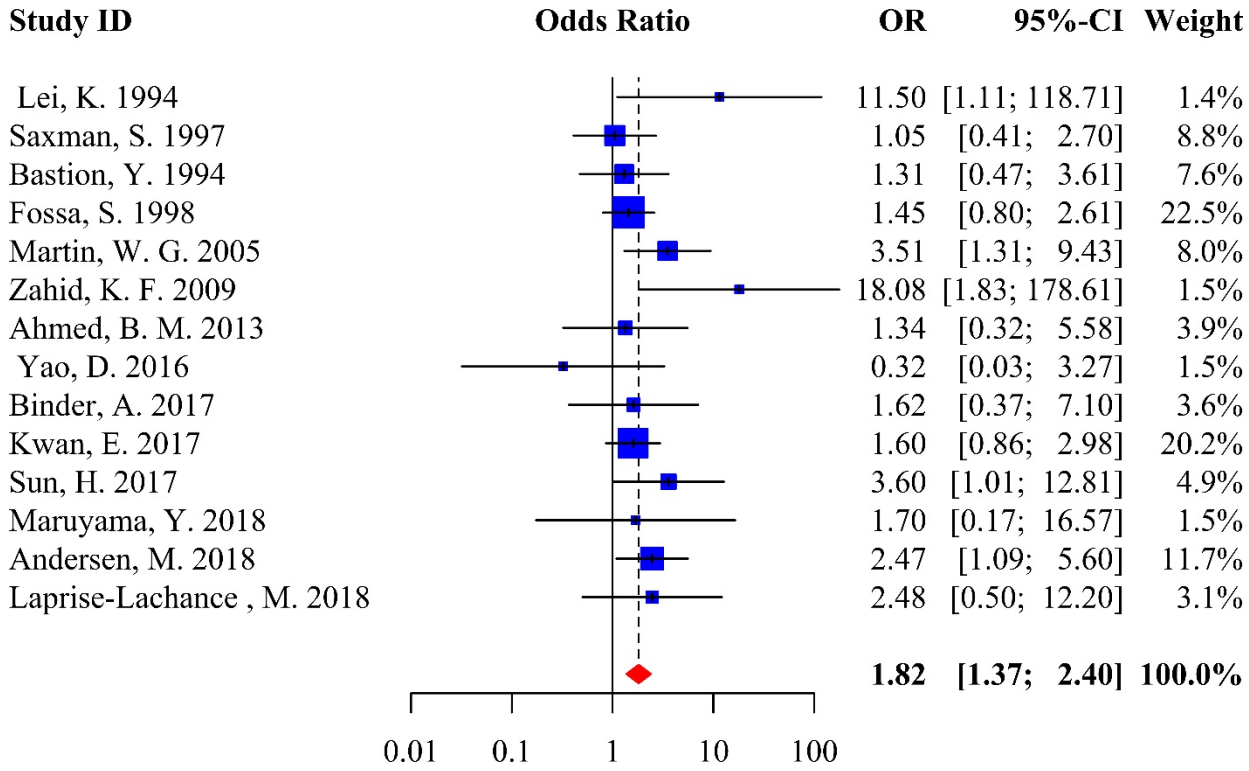

Figure 2: Forest Plot of odds ratio (OR) of the effect of concomitant CSF consumption on BPT incidence in cancer patients treated with bleomycin.

3.3. Sensitivity Analysis

The results of the leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Figure 3).

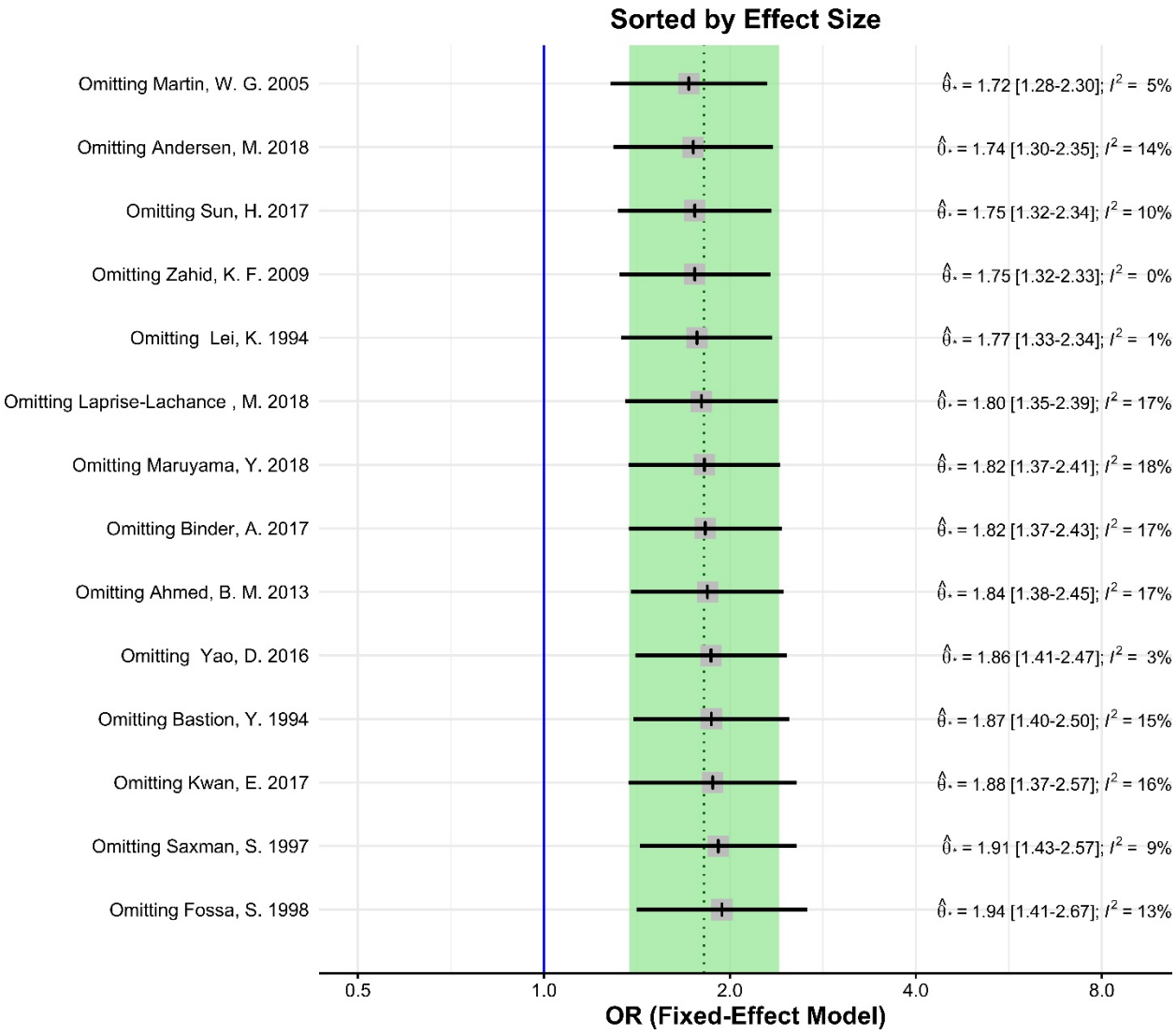

Figure 3: Leave-one-out sensitivity analysis

3.4. Subgroup Analysis and Meta-Regression

Regarding the place of the studies, the association between concomitant use of colony-stimulating factors and BPT was significant in Asia (OR=3.24, 95% CI: 1.23-8.57, p=0.0176), Europe (OR=1.65, 95% CI: 1.07-2.54, p=0.0236) and America (OR=1.79, 95% CI: 1.21-2.66, p=0.0039) (Table 2).

Table 2. Results of the subgroup meta-analysis

Factors		No. of Studies	OR (95% CI)	p-value	Heterogeneity	Between-subgroup difference
Continent	Asia	4 (3, 45, 53, 55)	3.24 (1.23-8.57)	0.0176	Q=5.08, p=0.167, I2=40.9%	Q=1.57 P= 0.4568
	Europe	3 (24, 54, 58)	1.65 (1.07-2.54)	0.0236	Q=1.34, p=0.5129, I2=0.0%	
	America	7 (4, 7, 26, 28, 51, 52, 57)	1.79 (1.21-2.66)	0.0039	Q=6.57, p=0.36, I2=8.7%	
Dosage of bleomycin (<200, ≥200)	Less than 200 mg	7 (3, 24, 26, 28, 54, 55, 58)	2.01 (1.40-2.88)	0.0002	Q=6.63, p=0.356, I2=9.5%	Q=0.35 P=0.5564
	More than 200 mg	2 (4, 45)	3.57 (0.23-56.41)	0.3656	Q=5.06, p=0.025, I2=80.2%	
Dosage of bleomycin (<150, >150)	Less than 150 mg	3 (3, 54, 58)	2.18 (1.18-4.03)	0.0131	Q=3.02, p=0.221, I2=33.7%	Q=0.35 P= 0.5564
	More than 150 mg	3 (4, 45, 53)	2.55 (0.49-13.26)	0.2655	Q=5.07, p=0.080, I2=60.5%	
Pulmonary functional test	Yes	6 (3, 7, 28, 53, 55, 58)	1.96 (1.09- 3.53)	0.0239	Q=4.05, p=0.542, I2=0.0%	Q=0.00 P= 0.9628
	No	7 (4, 26, 45, 51, 52, 54, 57)	1.93 (1.32- 2.82)	0.0006	Q=9.75, p=0.136, I2=38.5%	
Type of	Cohort	9 (3, 4, 7, 28,	1.90 (1.31- 2.78)	0.0008	Q=11.48, p=0.176,	Q=1.86

study		45, 51-54)			I2=30.3%	P= 0.3944
	clinical trial	2 (24, 58)	1.41 (0.85-2.35)	0.1879	Q=0.03, p=0.866, I2=0.0%	
	case-control	3 (26, 55, 57)	2.55 (1.24-5.26)	0.0112	Q=1.19, p=0.553, I2=0.0%	
Cancer type	NHL	2 (3, 58)	2.98 (0.38- 23.54)	0.3051	Q=2.80, p=0.094, I2=64.3%	Q=2.19 P=0.3349
	GCT	5 (4, 24, 45, 52, 53)	1.53 (1.05- 2.24)	0.0266	Q=5.13, p=0.274, I2=22.1%	
	HL	5 (7, 26, 28, 51, 54)	2.48 (1.49- 4.16)	0.0005	Q=4.11, p=0.392, I2=2.6%	

With regard to the dosage of bleomycin (<200 mg,≥200 mg), unlike dosages over 200 mg, the dosage under 200 mg has a significant association between concomitant use of colony-stimulating factors and BPT (OR=2.01, 95% CI=1.40-2.88, p=0.0002) (Table 2).

If we consider 150 mg as the cut off for bleomycin dose, the association between concomitant use of colony-stimulating factors and BPT was significant for dosage under 150 mg (OR=2.18, 95% CI: 1.18-4.03, p=0.0131), but the association was not significant for dosage over 150 mg (OR=2.55, 95% CI: 0.49-13.26, p=0.2655) (Table 2).

Based on receiving the pulmonary functional test, the association between concomitant use of colony-stimulating factors and BPT was significant for both subgroups (Table 2).

The association between concomitant use of colony-stimulating factors and BPT was significant for a subgroup of cohort and case-control studies, but clinical trials did not show a significant association between concomitant use of colony-stimulating factors and BPT (Table 2).

The association between concomitant use of colony-stimulating factors and BPT was significant for HL and GCT diagnosis, but it was not significant for NHL and mixed HL and GCT (Table 2). Forest plot of subgroup analysis recorded in the supplementary material (Figure S2-S7).

The results of fitting a meta-regression did not show any significant association between the year and duration of the studies and the pooled effect size (Table 3).

Table 3: Results of meta-regression

source	Regression coefficient	95% CI for regression coefficient	p-value
Duration	0.0013	(-0.0023, 0.0050)	0.4647
Year	0.0120	(-0.0170 0.0410)	0.4187

3.5. Publication Bias

Egger and Begg tests and the funnel plot (Figure 4) did not provide substantial evidence on the publication bias (Egger: Intercept= 0.78, 95% CI: -0.5-2.06, p = 0.257; Begg: z=1.37, p = 0.171).

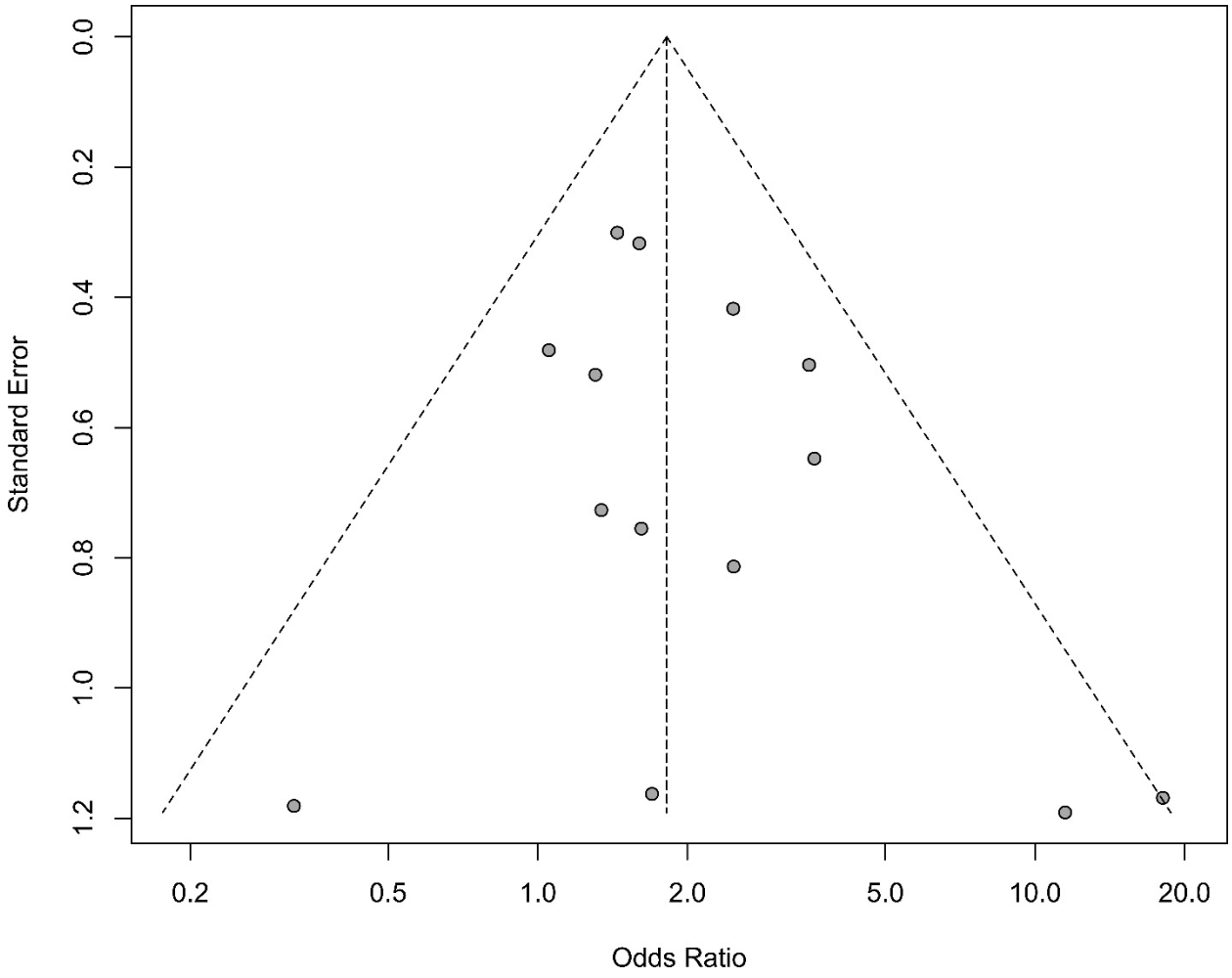

Figure 4:funnel plot

4. Discussion:

Bleomycin is a glycopeptide antitumor agent used in various conditions, including Hodgkin's and non-Hodgkin's lymphoma, germ cell tumors, and malignant pleural effusion. Genotoxicity, hyperpigmentation, neutropenia, and lung toxicity are adverse reactions of bleomycin, but the most dangerous is pulmonary toxicity (2-7, 9). BPT risk of incidence is exacerbated by different factors such as age, cumulative dose of bleomycin, other chemotherapy drugs, and colony-stimulating factors (4, 12, 13, 15, 18, 21-30). Some studies have reported higher BPT incidence and thus higher mortality in G-CSF co-administration, while others did not show any association (9). Several randomized and nonrandomized studies with different diagnoses include advanced testicular cancer, germ-cell tumors, Hodgkin and non-Hodgkin's lymphoma (NHL), and metastatic teratoma, reported no increase in BPT in the co-administration of filgrastim (7, 60).

Our subgroup analysis based on the cancer type showed OR of BPT incidence in HL patients to be 2.48 (1.49- 4.16), in GCT patients to be 1.53 (1.05- 2.24), and in NHL patients to be 2.98 (0.38- 23.54). Despite a higher pooled OR in HL than in GCT, the between-subgroup-difference in the meta-analysis subgrouped by cancer type was not significant. HL incidence peaks in two age groups: the first peak is in patients in their third decade of life, and the second is in patients older than 60 years old, while CGT mainly affects young men between 15-44 years old (61, 62). Moreover, Lauritsen et al. reported 2.3 times higher chance of BPT incidence in over-40-year-old patients; furthermore, a survey of patients, being 26 to 40 years old, did not find any relationship between age and BPT incidence (12, 13). Although we did not achieve enough data to perform subgroup analysis and meta-regression based on age, the observed higher BPT incidence in the HL patients compared to GCT patients could be related to the higher age of the HL patients. Nevertheless, it is notable that there is no definite claim on the effect of higher age on HL incidence. While age higher than 50 years old is claimed as a risk factor for HL incidence by the European Organization for Research and Treatment of Cancer (EORTC) but National Cancer Institue of Canada (NCIC), and Eastern Cooperative Oncology Group (ECOG) are reported age over 40 years as a risk factor for HL. German Hodgkin Study Group (GHSG) and National Comprehensive Cancer (NCCN) do not put higher age as a risk factor for HL incidence (61).

GCT and HL have a lower prevalence in economically underprivileged. On the other hand, NHL is rising in various areas, including Western Europe, Brazil, India, Japan and England. According to the continent, no significant difference between subgroups confirms that our findings can be generalized to different cancers and continents (63-65).

The cumulative dose of bleomycin is also one of the other BPT risk factors. Different cumulative dose cut-offs, including 170 mg and 400 mg, are suggested (15, 65). Also, cumulative doses higher than 150-200 mg have shown a higher incidence of the skin side effects of bleomycin in available studies. Here we performed subgroup analysis using both cumulative dose cut-offs of 150 mg and 200 mg (39). Despite no significant difference between cumulative bleomycin dose subgroups, the effect of G-CSF was not significant in doses higher than 150-200 mg. This can be justified by masking the adverse impact of G-CSF by the higher cumulative dose of bleomycin. Another explanation for this nonsignificant OR could be the low number of studies in these subgroups, making the confidence interval wide. However, we require more studies to have a more robust

suggestion on higher cumulative doses. Considering the overall OR, high OR of >150 mg and ≥200 mg subgroups, and no between-subgroups-difference, the nonsignificant confidence interval of higher doses subgroups as a result of low number and wide confidence interval of the included studies doesn't change this conclusion. Renal clearance is another important factor in bleomycin prescription since 80% of bleomycin eliminates through urine (14). Patients with renal dysfunction need dose adjustment for bleomycin. A 75% reduction in medication dose happens in patients with CrCl under 25 ml/min, and bleomycin should not be administered faster than 72 h (66). Co-administration of other chemotherapy drugs like cisplatin and gemcitabine are also risk factors for BPT (21, 22). Cisplatin, ifosfamide and methotrexate are chemotherapy drugs with obvious nephrotoxicity; other chemotherapeutic agents like gemcitabine and imatinib have also shown a mild risk of nephrotoxicity. Using these medications in combination with bleomycin in chemotherapy regimens like BEP and BOP/VIP-B and continuing these regimens to high cumulative doses could result in nephrotoxicity. Thus higher bleomycin concentration causes a higher incidence of BPT (24, 66). Moreover, as other drugs such as ACEIs and β-blockers can also lead to lung toxicity, these drugs affect BPT in concomitant use of CSFs and bleomycin is suggested to be investigated in future randomized clinical trials (RCTs) (54).

Paraclinical or functional test for BPT diagnosis has no difference in risk of BPT, although, in both subgroups, CSF use leads to an increase in the BPT risk. Since the paraclinical tests can help early detection of BPT, they may be helpful in the detection of early-stage of pulmonary toxicity. However, more investigations are required to establish the role of functional tests in this issue.

Using CSF concomitant with antibiotics for neutropenia does not change mortality risk and increases flu-like syndrome and bone pain. But, it can decrease hospitalization duration for more than ten days, reduce febrile neutropenia duration, and consequently, recovery time and decrease in the period of antibiotic therapy compared with antibiotics without CSF group. Moreover, both groups have no difference in thromboembolism risk (67).

Life expectancy and quality-adjusted life years (QALYs) for patients with advanced-stage Hodgkin lymphoma treated with ABVD and G-CSF as secondary prophylaxis for febrile neutropenia are 1.858 1.371, respectively, against 1.875 and 1.408 for patients with the equal condition without G-CSF. Patients without G-CSF secondary prophylaxis experience net benefit 0.037 QALYs (13.5 quality-adjusted days) and 0.017 years (6.2 days) for life expectancy, so without G-CSF strategy is better. Studies about cost-saving and use of G-CSF show that no use of G-CSF for 123 days in treatment with ABVD leads to saving £2000 for each patient. This cost is equivalent to Canadian dollar (CAD) 3406, whereas inflation. Avoiding G-CSF routinely prescription reduces CAD 10241 for each patient (32, 68, 69). A cost-effectiveness analysis in 2013 shows that QALYs become better in patients without G-CSF against G-CSF use 1.416 and 1.403, respectively, CAD 5089 cost save for patients with no G-CSF strategy. The mentioned study was done in patients with advanced-stage HL treated by ABVD with or without secondary prophylaxis use of G-CSF (70).

Previous guidelines recommended prophylaxis G-CSF for patients with 40% cut-off, but according to cost-effectiveness studies, a decrease of patients cut off to 20% for G-CSF prophylaxis looks rational (71-73).

G-CSF must be monitored when used with pneumotoxic chemotherapy drugs. The sudden rise of leucocyte, CRP, LDH, fever, and dyspnea might be a sign of pneumonitis. However, pulmonary function tests and chest radiographs should be performed to prove it. If pneumonitis is established, a pulse of steroids must be prescribed immediately (74). At this condition, 0.75-1mg/kg prednisolone is used for 4-8 weeks, then tapered down in additional 4-6 months. Patients' symptoms become better for a short time, but they may relapse during taper down. Imatinib mesylate can cure patients with severe BPT treated by ABVD, leading to renal impairment. Also, nilotinib, montelukast, gefitinib, pravastatin, and sirolimus have shown encouraging results (66, 75).

Two mechanisms are suggested for the exacerbating effect of G-CSF on pulmonary toxicity during chemotherapy. The first one is the rising number of activated neutrophils in place and reactive oxygen caused by them and the second one is an increase in the number of leukocytes during the treatment (76). *In-vitro* studies showed bleomycin stimulates a type II pneumocyte cell line (A549), which increases monocyte and neutrophil chemotactic activities. Also, bleomycin exposure resulted in a significant increase in granulocyte colony-stimulating factors concentration in A549 cells supernatant (77). Moreover, new animal studies suggest mechanisms for the protective role of G-CSF in BPT; however, these mechanisms cannot be generalized to humans. Therefore, human studies are required for further mechanism detection and finding the best treatment (78-80).

Binder, A. F. et al. reported that BPT has a higher incidence in the first 3-6 months in patients using bleomycin and G-CSF together. However, it has a higher incidence in the first 6-9 months in patients treated with bleomycin alone. This phenomenon suggests that contaminant use of G-CSF accelerates BPT incidence in BPT susceptible patients (7).

According to three studies, BPT has no adverse effects on survival outcomes, including progression-free survival (PFS) and overall survival (OS). It is also mentioned that bleomycin discontinuation has no negative impact on survival outcome; however, a conference abstract reported lower OS in patients discontinuing bleomycin (28, 46, 53, 54).

The most important limitations of this study lie in the fact that most of the included studies were uncontrolled and retrospective observational studies on different cancer types and different chemotherapy regimens, performed in different countries. Also, there is a variety in definition of BPT and tests performed for BPT diagnosis. However, considering low heterogenicity explained by an I^2 of 10.7% and no significant between-subgroup-difference, this limitation could also be a strength of this study since the results can be generalized to different included cancer types and regimens. Among Contradictory statements on the presence of G-CSF effect on BPT, which is crucial in deciding patient treatment strategy, this study is the first systematic review and meta-analysis trying to pool the evidence and conclude the debate with a final result. The high number of pooled patients in this study compared to previous studies makes the results more reliable. However, we suggest future controlled clinical trials to have a broader sight of the obtained findings.

In conclusion, our findings show a considerable 1.82 relative higher odds in BPT incidence by concomitant use of G-CSF, which the physicians should consider at the time of G-CSF prescription besides bleomycin. The choice of not prescribing G-CSF in a susceptible patient could mean lower side effects and medical costs, and finally, higher patient quality of life.

5. Conclusion:

Results of our study show that concomitant use of colony-stimulating factors and bleomycin increase the risk of BPT. Subgroup analysis shows no significant differences between different subgroups,s including Continents (America, Europe, and Asia), cancer types (HL, NHL, and GCT), type of studies (cohort, clinical trial, and case-control), use of functional pulmonary tests for BPT diagnosis and cumulative bleomycin dosages. The strategy of not using G-CSF will reduce patient costs but increase hospitalization time and reduce life expectancy due to febrile neutropenia. This strategy makes no significant change in QALYand mortality induced by febrile neutropenia. Overall, it is necessary to consider the points mentioned above in choosing the best treatment strategy for the patient.

References:
1. Bolzán AD, Bianchi MS. DNA and chromosome damage induced by bleomycin in mammalian cells: An update. Mutat Res Rev Mutat Res. 2018;775:51-62.
2. Kong J, Yi L, Xiong Y, Huang Y, Yang D, Yan X, et al. The discovery and development of microbial bleomycin analogues. Appl Microbiol Biotechnol. 2018;102(16):6791-8.
3. Lei KI, Leung WT, Johnson PJ. Serious pulmonary complications in patients receiving recombinant granulocyte colony-stimulating factor during BACOP chemotherapy for aggressive non-Hodgkin's lymphoma. Br J Cancer. 1994;70(5):1009-13. Epub 1994/11/01.
4. Saxman SB, Nichols CR, Einhorn LH. Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. Chest. 1997;111(3):657-60. Epub 1997/03/01.
5. Saitta P, Krishnamurthy K, Brown LH. Bleomycin in dermatology: a review of intralesional applications. Dermatol Surg. 2008;34(10):1299-313.
6. Marri PR, Ristow K, Habermann TM, Rodriguez V, Ansell SM. Older patients and risk of developing and dying from bleomycin-induced lung toxicity. J Clin Oncol. 2014;32(15).
7. Binder AF, Rai S, Steinberg A. The use of filgrastim in patients with hodgkin lymphoma receiving ABVD. Int J Hematol Oncol Stem Cell Res. 2017;11(4):286-92.
8. Hansen SW. Autonomic neuropathy after treatment with cisplatin, vinblastine, and bleomycin for germ cell cancer. BMJ. 1990;300(6723):511.
9. Azambuja E, Fleck JF, Batista RG, Barreto SM. Bleomycin lung toxicity: who are the patients with increased risk? Pulm Pharmacol Ther. 2005;18(5):363-6.
10. Mehta HM, Malandra M, Corey SJ. G-csf and gm-csf in neutropenia. J Immunol. 2015;195(4):1341-9.
11. Cochran WG. Some methods for strengthening the common χ 2 tests. Biometrics. 1954;10(4):417-51.
12. Lauritsen J, Kier MGG, Bandak M, Mortensen MS, Thomsen FB, Mortensen J, et al. Pulmonary function in patients with germ cell cancer treated with bleomycin, etoposide, and cisplatin. J Clin Oncol. 2016;34(13):1492-9.
13. O'sullivan J, Huddart R, Norman A, Nicholls J, Dearnaley D, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol. 2003;14(1):91-6.
14. Sleijfer S, Van der Mark T, Koops HS, Mulder N. Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. Eur J Cancer. 1996;32(3):550-2.
15. Blum RH, Carter SK, Agre K. A clinical review of bleomycin—a new antineoplastic agent. Cancer. 1973;31(4):903-14.
16. Hirsch A, Vander Els N, Straus DJ, Gomez EG, Leung D, Portlock CS, et al. Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease. J Clin Oncol. 1996;14(4):1297-305.
17. Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001;120(2):617-24.
18. Maruyama Y, Sadahira T, Araki M, Mitsui Y, Wada K, Edamura K, et al. Comparison of the predictive value among inflammation-based scoring systems for bleomycin pulmonary toxicity in patients with germ cell tumors. International Journal of Urology. 2019;26(8):813-9.
19. Chandler DB. Possible mechanisms of bleomycin-induced fibrosis. Clin Chest Med. 1990;11(1):21-30.
20. Tryka AF, Skornik WA, Godleski JJ, Brain JD. Potentiation of bleomycin-induced lung injury by exposure to 70% oxygen: morphologic assessment. Am Rev Respir Dis. 1982;126(6):1074-9.
21. Haugnes HS, Aass N, Fosså SD, Dahl O, Brydøy M, Aasebø U, et al. Pulmonary function in long-term survivors of testicular cancer. J Clin Oncol. 2009;27(17):2779-86.
22. Macann A, Bredenfeld H, Müller R-P, Diehl V, Engert A, Eich HT. Radiotherapy does not influence the severe pulmonary toxicity observed with the administration of gemcitabine and bleomycin

in patients with advanced-stage Hodgkin's lymphoma treated with the BAGCOPP regimen: a report by the German Hodgkin's Lymphoma Study Group. Int J Radiat Oncol Biol Phys. 2008;70(1):161-5.
23. Evens AM, Cilley J, Ortiz T, Gounder M, Hou N, Rademaker A, et al. G-CSF is not necessary to maintain over 99% dose–intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol. 2007;137(6):545-52.
24. Fosså SD, Kaye SB, Mead GM, Cullen M, De Wit R, Bodrogi I, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. J Clin Oncol. 1998;16(2):716-
25. Lazo JS, Merrill WW, Pham ET, Lynch TJ, McCallister J, Ingbar D. Bleomycin hydrolase activity in pulmonary cells. J Pharmacol Exp Ther. 1984;231(3):583-8.
26. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE, Ansell SM. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol. 2005;23(30):7614-20. Epub 2005/09/28.
27. Stamatoullas A, Brice P, Bouabdallah R, Mareschal S, Camus V, Rahal I, et al. Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. Br J Haematol. 2015;170(2):179-84.
28. Sun H, Atenafu EG, Tsang R, Kukreti V, Marras TK, Crump M, et al. Bleomycin pulmonary toxicity does not adversely affect the outcome of patients with Hodgkin lymphoma. Leuk Lymphoma. 2017;58(11):2607-14.
29. Wedgwood A, Younes A. Prophylactic use of filgrastim with ABVD and BEACOPP chemotherapy regimens for Hodgkin lymphoma. Clin Lymphoma Myeloma. 2007;8:S63-S6.
30. Younes A, Fayad L, Romaguera J, Pro B, Goy A, Wang M. Safety and efficacy of once-per-cycle pegfilgrastim in support of ABVD chemotherapy in patients with Hodgkin lymphoma. Eur J Cancer. 2006;42(17):2976-81.
31. Haim N, Shulman K, Goldberg H, Tsalic M. The safety of full-dose chemotherapy with secondary prophylactic granulocyte colony stimulating factor (G-CSF) following a prior cycle with febrile neutropenia. Med Oncol. 2005;22(3):229-32.
32. Minuk LA, Monkman K, Chin-Yee IH, Lazo-Langner A, Bhagirath V, Chin-Yee BH, et al. Treatment of Hodgkin lymphoma with adriamycin, bleomycin, vinblastine and dacarbazine without routine granulocyte-colony stimulating factor support does not increase the risk of febrile neutropenia: a prospective cohort study. Leukemia & lymphoma. 2012;53(1):57-63.
33. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.
34. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
35. Binder AF, Rai S, Steinberg A. The Use of Filgrastim in Patients with Hodgkin Lymphoma Receiving ABVD. Int J Hematol Oncol Stem Cell Res. 2017;11(4):286.
36. Tarsilla M. Cochrane handbook for systematic reviews of interventions. Journal of Multidisciplinary Evaluation. 2008;6(14):142-8.
37. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing meta-analysis with R: A hands-on guide. 2019.
38. Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Res Synth Methods. 2010;1(2):112-25.
39. MS. C, SN. G, B. S, Goldberg., A. H, Deshpande. Miscellaneous Chemotherapeutic Agents. In: VT. DJ, TS. L, SA. R, editors. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 10 ed. United States of America: Philadelphia: Wolters Kluwer,[2015], Philadelphia, EEUU; 2015. p. 267-77.
40. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

41. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994:1088-101.
42. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evidence-based mental health. 2019;22(4):153-60.
43. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1-48.
44. Iki S, Yoshinaga K, Ohbayashi Y, Urabe A. Cytotoxic drug-induced pneumonia and possible augmentation by G-CSF - clinical attention. Ann Hematol. 1993;66(4):217-8.
45. Zahid KF, Muzaffar N, Usman M, Uddin N. Risk factors for bleomycin induced pulmonary toxicity in germ cell tumor patients. Eur J Cancer Suppl. 2009;7(2-3):448.
46. Tran B, Moore MJ, Amir E, Jewett MA, Anson-Cartwright L, Sturgeon JFG, et al. Impact of renal impairment and granulocyte colony stimulating factor (GCSF) on bleomycin-induced pneumonitis (bleo lung), febrile neutropenia (FN), and survival in patients (pts) with germ cell tumor (GCT) treated with chemotherapy (chemo). J Clin Oncol. 2012;30(5).
47. Alexandre M, Luis A, Duarte I, Esteves S, Guimarães A, Moreira A, et al. Bleomycin lung toxicity in patients with male germ cell cancer. Eur J Cancer. 2013;49((Alexandre M.; Luis A.; Guimarães A.; Moreira A.; Brito M.) Instituto Oncologia Lisboa, Medical Oncology, Lisboa, Portugal):S667.
48. Santos J, Carvalho S, Esteves S, Gomes da Silva M. Acute pulmonary toxicity of bleomycin-incidence and risk factors in a series of Hodgkin Lymphoma (HL) patients treated in a single center. Haematologica. 2013;98((Santos J.; Carvalho S.; Esteves S.; Gomes da Silva M.) Instituto Português de Oncologia de Lisboa Francisco, Gentil, Portugal):62.
49. Stamatoullas A, Brice P, Bouabdallah R, Camus V, Rahal I, Franchi P, et al. Outcome of patients aged over 60 with classical hodgkin lymphoma treated with ABVD. Haematologica. 2014;99((Stamatoullas A.; Camus V.; Lanic H.; Tilly H.) Hematology, Centre Henri Becquerel, Rouen, France):397.
50. Ko JJ, Asif T, Li H, Alimohamed NS, Nguyen TP, Heng DYC. Use of primary G-CSF and its impact on febrile neutropenia, hospitalization, dose delivery, and survival in patients with metastatic testicular germ-cell tumour (MT-GCT). J Clin Oncol. 2015;33(15).
51. Yao D, Janakiram M, O'Brien TE. Pegfilgrastim use and risk of bleomycin induced pulmonary toxicity in hodgkin lymphoma. Biometrics. 2016;128(22).
52. Kwan EM, Beck S, Amir E, Jewett MA, Sturgeon JF, Anson-Cartwright L, et al. Impact of Granulocyte-colony Stimulating Factor on Bleomycin-induced Pneumonitis in Chemotherapy-treated Germ Cell Tumors. Clin Genitourin Cancer. 2017. Epub 2017/09/26.
53. Maruyama Y, Sadahira T, Mitsui Y, Araki M, Wada K, Tanimoto R, et al. Prognostic impact of bleomycin pulmonary toxicity on the outcomes of patients with germ cell tumors. Med Oncol. 2018;35(6).
54. Andersen MD, Kamper P, d'Amore A, Clausen M, Bentzen H, d'Amore F. The incidence of bleomycin induced lung toxicity is increased in Hodgkin lymphoma patients over 45 years exposed to granulocyte-colony stimulating growth factor†. Leuk Lymphoma. 2019;60(4):927-33.
55. Ahmed BM, Al-Zakwani IS. Incidence, outcome and predictors of bleomycin pulmonary toxicity in a university hospital in Oman. J Oncol Pharm Pract. 2013;19(1):3-7. Epub 2012/04/17.
56. Tayshetye P, Padhi P, Rao R, Sklyar TY, Chilkulwar A, Miller R, et al. Bleomycin-induced pulmonary toxicity: A retrospective review of incidence and risk factors. J Clin Oncol. 2018;36(15).
57. Laprise-Lachance M, Lemieux P, Gregoire JP. Risk of pulmonary toxicity of bleomycin and filgrastim. J Oncol Pharm Pract. 2019;25(7):1638-44.
58. Bastion Y, Reyes F, Bosly A, Gisselbrecht C, Yver A, Gilles E, et al. Possible toxicity with the association of G-CSF and bleomycin. Lancet. 1994;343(8907):1221-2.
59. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372.

60. Neumann TA, Foote M. The safety profile of filgrastim and pegfilgrastim. Milestones in Drug Therapy2012. p. 395-408.
61. Momotow J, Borchmann S, Eichenauer DA, Engert A, Sasse S. Hodgkin Lymphoma—Review on Pathogenesis, Diagnosis, Current and Future Treatment Approaches for Adult Patients. J Clin Med. 2021;10(5):1125.
62. Batool A, Karimi N, Wu X-N, Chen S-R, Liu Y-X. Testicular germ cell tumor: a comprehensive review. Cell Mol Life Sci. 2019;76(9):1713-27.
63. Shankland KR, Armitage JO, Hancock BW. Non-hodgkin lymphoma. Lancet. 2012;380(9844):848-57.
64. Dieckmann K-P, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. World J Urol. 2004;22(1):2-14.
65. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. Crit Rev Oncol Hematol. 2013;85(2):216-37.
66. Li Y, Fu S, Hu W, Liu J, Finkel K, Gershenson D, et al. Systemic anticancer therapy in gynecological cancer patients with renal dysfunction. Int J Gynecol Cancer. 2007;17(4).
67. Mhaskar R, Clark OAC, Lyman G, Botrel TEA, Paladini LM, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev. 2014(10).
68. Graczyk J, Cheung MC, Buckstein R, Chan K. Granulocyte colony-stimulating factor as secondary prophylaxis of febrile neutropenia in the management of advanced-stage Hodgkin lymphoma treated with adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy: a decision analysis. Leukemia & lymphoma. 2014;55(1):56-62.
69. Nangalia J, Smith H, Wimperis JZ. Isolated neutropenia during ABVD chemotherapy for Hodgkin lymphoma does not require growth factor support. Leukemia & lymphoma. 2008;49(8):1530-6.
70. Cheung M, Prica A, Graczyk J, Buckstein R, Chan K. Granulocyte colony-stimulating factor in secondary prophylaxis for advanced-stage Hodgkin lymphoma treated with ABVD chemotherapy: A cost-effectiveness analysis. Leukemia & lymphoma. 2016;57(8):1865-75.
71. Ozer H, Armitage JO, Bennett CL, Crawford J, Demetri GD, Pizzo PA, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol. 2000;18(20):3558-85.
72. Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol. 2005;23(6):1178-84.
73. Timmer-Bonte JN, Adang EM, Smit HJ, Biesma B, Wilschut FA, Bootsma GP, et al. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in small-cell lung cancer. J Clin Oncol. 2006;24(19):2991-7.
74. Niitsu N, Iki S, Muroi K, Motomura S, Murakami M, Takeyama H, et al. Interstitial pneumonia in patients receiving granulocyte colony-stimulating factor during chemotherapy: survey in Japan 1991-96. Br J Cancer. 1997;76(12):1661-6.
75. Madabhavi I, Modi G, Patel A, Anand A, Panchal H, Parikh S. Pulmonary toxicity following bleomycin use: a single-center experience. J Cancer Res Ther. 2017;13(3):466.
76. Yokose N, Ogata K, Tamura H, An E, Nakamura K, Kamikubo K, et al. Pulmonary toxicity after granulocyte colony-stimulating factor-combined chemotherapy for non-Hodgkin's lymphoma. Br J Cancer. 1998;77(12):2286-90.
77. Sato E, Koyama S, Masubuchi T, Takamizawa A, Kubo K, Nagai S, et al. American Journal of Physiology - Lung Cellular and Molecular Physiology. Am J Physiol. 1999;276(6 20-6):L941-L50.
78. Zhao F-y, Cheng T-y, Yang L, Huang Y-h, Li C, Han J-z, et al. G-CSF inhibits pulmonary fibrosis by promoting BMSC homing to the lungs via SDF-1/CXCR4 chemotaxis. Scientific reports. 2020;10(1):1-11.
79. Zhang F, Zhang L, Jiang H-s, Chen X-y, Zhang Y, Li H-p, et al. Mobilization of bone marrow cells by CSF3 protects mice from bleomycin-induced lung injury. Respiration. 2011;82(4):358-68.

80. Moore BB, Coffey MJ, Christensen P, Sitterding S, Ngan R, Wilke CA, et al. GM-CSF regulates bleomycin-induced pulmonary fibrosis via a prostaglandin-dependent mechanism. J Immunol. 2000;165(7):4032-9.